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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,475	01/22/2002	Alexander Gaiger	210121.494C2	3551

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EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,475	GAIGER ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 7-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

The request filed on 11/30/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 10/057,475 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 1-26 are pending.

Claims 1-5 and 7-26 have been withdrawn.

Claim 6 has been amended by Applicant.

Claim 6 is currently under consideration.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

The following Office Action contains New Rejections.

Rejections Withdrawn

The rejection of claim 6 under 35 U.S.C 112 first paragraph, for failing to comply with the enablement requirement, is withdrawn. However, it is noted that new rejections of claim 6, addressing the change of scope due to amendments, under 35 U.S.C. 112, first paragraph, are set-forth below.

Response to Arguments

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claim 6 under 35 U.S.C., second paragraph, is maintained for the reasons found in the Office Action of 5/31/06 and the reasons set-forth below.

Claim 6 has been rejected for reciting "a predetermined cutoff value". The claim is indefinite because it is not clear exactly how the exact numeric value of the "predetermined cutoff value" is to be determined. This renders the claim indefinite because the method steps of obtaining a "predetermined cutoff value" are not defined by the claim and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined. Further, without reciting how one is to obtain a predetermined cut-off value, the claims are incomplete for omitting the essential step comprising determining a cut-off value, such omission amounts to a gap between the steps (see MPEP § 2172.01).

In response to the Office Action of 5/31/06, Applicant states that the claim has been amended to recite that when an amount of polypeptide detected is greater than the predetermined cut-off value, this is indicative of the presence of lymphoma in a patient. Further, Applicant argues that since there are multiple ways in which one could determine a predetermined cut-off value, there is no need to restrict the claimed invention to defining how one is to obtain said predetermined cutoff value. Applicant further cites case law that indicates the primary purpose of the indefiniteness requirement is "to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty to their respective rights". Applicant further states to incorporate a specific means for determining a predetermined cut-off value into the claim would allow a third party the opportunity to determine a cut-off value by an alternative but equivalent known technique other than that specifically

incorporated into the claim, and thereby exploit Applicant's discovery that the claimed polypeptide is an effective diagnostic marker for lymphoma, all while practicing outside the scope of protection to which the Examiner asserts that Applicants are entitled. Applicant further states that in this instance, the disadvantage is placed on Applicants and the advantage on others, which is submitted to be inconsistent with the spirit and scope of the definiteness requirement as stated by the Federal Circuit. Applicant further states that what is important in the context of the claimed method is the comparison between the measured amount of the polypeptide and a pre-determined control value, not the specific manner used for arriving at the pre-determined control value. Applicant further states that the determination of a suitable control cut-off value for comparison of diagnostic markers is not in any way a concept or practice that is difficult for an artisan of skill in the diagnostic arts to understand or implement. Further, Applicant states that it would be well recognized that different cut-off values may have different numeric values and/or use different measures, depending on the specific approach employed, while still being suitable comparative cut-off values in the context of the claimed invention for detecting lymphomas.

The amendments to claim 6 and the arguments found in the RCE of 11/30/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that since there are multiple ways in which one could determine a predetermined cut-off value there is no need to restrict the claimed invention to defining how one is to obtain said predetermined cutoff value, the claims provide no guidance of how one is to obtain a predetermined cutoff value. Without providing such guidance,

the method is incomplete for missing a step. Further, without reciting the missing step of determining a cut-off value, the metes and bounds of the method are unclear. In regards to case law that indicates the primary purpose of the indefiniteness requirement is "to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty to their respective rights", without reciting how one is to obtain a predetermined cut-off value the claimed method would provide unreasonable advantages to the patentee and disadvantages to others arising from uncertainty to their respective rights. In regards to the statement that incorporating a specific means for determining a predetermined cut-off value into the claim would allow a third party the opportunity to determine a cut-off value by an alternative but equivalent known technique other than that specifically incorporated into the claim, and thereby exploit Applicant's discovery that the claimed polypeptide is an effective diagnostic marker for lymphoma, all while practicing outside the scope of protection to which the Examiner asserts that Applicants are entitled, it is suggested that Applicant may want to draft claims in a manner that compares amounts of polypeptides between two specific samples. For instant, rather than comparing an amount to a "predetermined cutoff value", it is suggested Applicant may want to compare an amount in one specific sample (such as a lymph node sample from a patient suspected of having lymphoma) to an amount in another specific sample (such as a lymph node sample from a healthy subject). In regards to the argument that what is important in the context of the claimed method is the comparison between the measured amount of the polypeptide and a pre-determined control value, not the specific manner used for arriving at the pre-

determined control value, the claim remains indefinite for the reasons described above. What is important does not affect the indefiniteness of the claim. In regards to the argument that the determination of a suitable control cut-off value for comparison of diagnostic markers is not in any way a concept or practice that is difficult for an artisan of skill in the diagnostic arts to understand or implement, without a recited method step for determining the cutoff value one would not know how to determine said cutoff value. In regards to the argument that it would be well recognized that different cut-off values may have different numeric values and/or use different measures, depending on the specific approach employed, while still being suitable comparative cut-off values in the context of the claimed invention for detecting lymphomas, what *may* be a "suitable" cutoff value is not the basis of this rejection. This rejection is based on how one is to determine a cutoff value.

New Rejections

35 USC § 112, first paragraph (Written Description)

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claim is inclusive of a genus of binding agents that bind to polypeptides encoded by the nucleic acid comprising the sequence set forth in SEQ ID NO:10582 or a complement thereof. However, the written

description in this case only sets forth binding agents that bind to polypeptides comprising the sequence set-forth in SEQ ID NO:9611. The specification does not disclose any other binding agents that bind to polypeptides encoded by the nucleic acid comprising the sequence set forth in SEQ ID NO:10582 or a complement thereof as broadly encompassed in the claim. Further, it is noted that the specification teaches SEQ ID NO:10582 comprises a sequences that encodes the polypeptide set-forth in SEQ ID NO:9611 (see Figure 9 and Example 12, in particular). However, the specification does not provide a written description of the genus of polypeptides encoded by the nucleic acid comprising the sequence set forth in SEQ ID NO:10582 or a complement thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient

descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of binding agents that encompass the genus nor does it provide a description of structural features that are common to said binding agents. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure SEQ I DNO:10,582 and SEQ ID NO:9,611 is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a binding agent wherein said binding agent binds to polypeptides comprising the sequence set-forth in SEQ ID NO:9611, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, first paragraph (Enablement Rejection)

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of lymphoma in a patient comprising detecting levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from said patient and comparing said levels to the levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from a subject that does not have lymphoma, wherein higher levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from said patient, as compared to levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from a subject that does not have lymphoma, indicates that said patient has lymphoma, the specification does not reasonably provide enablement for a method for detecting the presence of

lymphoma in a subject by contacting any biological sample from said subject with a binding agent that binds to any polypeptide encoded by the nucleic acid comprising the sequence set-forth in SEQ ID NO:10, 582 or a complement thereof, and comparing the amount of polypeptide to any predetermined cutoff value, wherein an amount of polypeptide that is greater than any predetermined cutoff value is indicative of, in every way, the presence of lymphoma in the patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to a method for detecting the presence of lymphoma in a subject by contacting any biological sample from said subject with a binding agent that binds to any polypeptide encoded by the nucleic acid comprising the sequence set-forth in SEQ ID NO:10,582 or a complement thereof, and comparing the amount of polypeptide to any predetermined cutoff value, wherein an amount of polypeptide that is greater than any predetermined cutoff value is indicative of, in any way, the presence of lymphoma in the patient. This broadly claimed method includes

methods wherein the detected polypeptide is substantially different than a polypeptide comprising the sequence set-forth in SEQ ID NO:9611 (such as polypeptides encoded by complements of SEQ ID NO:10,582). Further, this broadly claimed method includes any using any biological sample. Further, this broadly claimed method includes predetermined cutoff values of zero, wherein the detection of *a single polypeptide* encoded by the nucleic acid comprising the sequence set-forth in SEQ ID NO:10,582 or a complement thereof would be indicative of lymphoma. Further, this broadly claimed method includes methods wherein an amount of polypeptide that is greater than a predetermined cut-off value is indicative of the presence of lymphoma in the patient in that a greater amount indicates that the patient *has* lymphoma or that the greater amount indicates that the patient *does not have* lymphoma.

The specification teaches that the polynucleotide sequence SEQ ID NO:10,582 was identified, using a combination of PCR subtracted cDNA libraries, microarray analyses, and RealTime PCR, as a gene with a similar tissue expression profile to CD20 and CD52 in lymphomas (Example 5, in particular). The specification further teaches that SEQ ID NO:10,582 is also termed Ly1448 (see Figure 9 and paragraph 576, in particular). The specification further teaches that higher levels of antibodies that interact with a polypeptide encoded by SEQ ID NO:10,582, the polypeptide comprising the amino acid sequence set-forth in SEQ ID NO:9611, in the sera of lymphoma patients as compared to normal controls (see Figure 31 and Example 13, in particular), which indicates that a polypeptide comprising the polynucleotide sequence set-forth in SEQ ID NO:9611 could be used as a diagnostic marker for lymphomas. It is further

noted that antibodies specific for polypeptide comprising the polynucleotide sequence set-forth in SEQ ID NO:9611 were detected in all normal serum samples tested.

If a molecule such as a protein encoded by a nucleic acid comprising the sequence set forth in SEQ ID NO:10,582 or a complement thereof is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714,

see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the peptides in any diagnostic setting without undue experimentation.

The Applicants have presented sufficient data demonstrating that detection of a polypeptide comprising SEQ ID NO:9611 could be used as a diagnostic marker for lymphomas; however, the Applicants have not demonstrated that expression of a polypeptide encoded by *complements of* the sequence set forth in SEQ ID NO:10,582 would be used as a marker for lymphomas with any predictability of success.

Further, Applicants have presented sufficient data demonstrating that detection of a polypeptide comprising SEQ ID NO:9611 in lymphoid cells could diagnose lymphomas; however, the Applicants have not demonstrated that detection of a polypeptide comprising SEQ ID NO:9611 in just any biological sample would predictably be indicative of lymphomas.

Further, Applicants have presented sufficient data demonstrating that *higher* levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from a patient, as compared to levels of polypeptides comprising the sequence set-forth in SEQ ID NO:9611 in lymphoid samples from a subject that does not have lymphoma, indicates that said patient has lymphoma. However, Applicants

have also demonstrated that "just any" predetermined cutoff level would not function with the claimed invention because the specification discloses that all healthy individuals examined were found to have antibodies specific for polypeptides comprising the sequence set-forth in SEQ ID NO:9611, which indicates that all healthy individuals express polypeptides comprising the sequence set-forth in SEQ ID NO:9611. Therefore, claimed invention would not predictably function with any success if the "predetermined cutoff level" is below that found in samples of normal patients.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for detecting the presence of lymphoma in a subject by contacting any biological sample from said subject with a binding agent that binds to any polypeptide encoded by the nucleic acid comprising the sequence set-forth in SEQ ID NO:10,582 or a complement thereof, and comparing the amount of polypeptide to any predetermined cutoff value, wherein an amount of polypeptide that is greater than any predetermined cutoff value is indicative of, in any way, the presence of lymphoma in the patient, and Applicant has not enabled said method because it has not been shown that higher levels of polypeptides encoded by the nucleic acid comprising the sequence set-forth in SEQ ID NO:10,582 or a complement thereof in just any sample, as compared to just any predetermined cutoff

level, would predictably be indicative, in every way, of lymphomas with an expectation of success.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

New Objection

Claim 6 is objected to because of an apparent typographical error. Claim 6 recites: "...greater than the predetermined cut-off values...". It is suspected Applicant intended claim 6 to recite: "...greater than the predetermined cut-off value~~s~~...". Proper correction is required.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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